41. (New) The vaccine of claim 8 wherein the vaccine vector comprises a nucleic acid molecule which encodes a polypeptide which has been modified from SEQ ID NO:2 by conservative amino acid substitution without loss of immunogenicity, wherein said modified polypeptide is at least 75% identical in amino acid sequence to SEQ ID NO:2.

REMARKS

I. Amendments

The first page of the claims has been amended to begin with "What is claimed is:".

Page 7 of the specification has been amended to delete reference at line 15 to the web address "http://chlamydia-www.berkeley.edu:4231/".

Page 22 has been amended to provide an updated address for the American Type Culture Collection at line 10.

The Examples have been amended at page 48 and 49, to identify sequences specifically by SEQ ID NOs. It is clear that SEQ ID NO:1 encodes the outer membrane protein (OMP) expressed from plasmid construct pCAmgp002.

Claims 8 to 11 have been amended, and new claims 38-41 added, to more clearly and particularly claim the invention, as described in more detail below. Because these amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

Claims 8 and 10 have been reformatted to independent claim format by explicitly reciting the nucleic acid of cancelled claim 1. The claims have been further amended:

- to replace --to improve its immunogenicity-- (originally in claim 1) with --without loss of immunogenicity--. Basis for this amendment is found at least at line 33 of page 11 to line 2 of page 12, and lines 3-8 of page 13 of the specification.
- to state in parts (c) that the modification is by conservative amino acid substitution. Basis for this amendment is found at least at lines 7-22 of page 12 of the specification.
- to specify that the nucleic acid molecule is --operatively linked to one or more control sequences for expression of the polypeptide in a mammalian cell--. Basis for this amendment is found at least at page 25 lines 7-9; page 25 line 33 to page 26 line 2; page 29 lines 17-30, as well as Example 2 where the CMV promoter is used to drive expression of the nucleic acids of the invention in mice.

Claim 8 has been further amended to state --wherein the vaccine vector comprises a nucleic acid molecule--. Basis for this amendment is found at least at page 24 line 29 to page 25 line 3; page 25 lines 6-9; page 25 lines 29-30; page 26 line 28 to page 27 line 7; page 27 lines 17-28; page 28 lines 3-7 and lines 10-17; and page 28 lines 18-20.

Claim 8 has also been amended to specify that the nucleic acid molecule is --integrated and expressed in a bacterial cell suitable for use as a vaccine vector--. Basis for this amendment is found at least at page 27 lines 2-7, where the nucleic acids are described as being inserted into the viral genome for expression in mammalian cells, page 28 lines 18-19, where the nucleic acids are described as being inserted into the bacterial genome in bacterial vectors, as well as page 29 lines 7-11.

Claim 8 has also been amended to remove the "optional" feature to new, dependent claim 38 (see below).

Claim 10 has been further amended to recite that the composition comprises a carrier --or diluent suitable for use in a vaccine--. The amendment is supported at least at page 9 lines 18-25; page 25 lines 9-11; page 28 lines 25-28; page 46 line 27 to page 47 line 5 of the specification.

Claim 11 has been re-worded so that the claim is drawn to a vaccine which further comprises a pharmaceutically acceptable carrier, rather than to a pharmaceutical composition comprising the vaccine and carrier.

Claim 38 has been added to capture the "optional" feature originally found in claim 8. The language has been revised to clarify that the additional polypeptide enhances the immune response to the polypeptide originally recited in claim 1. Claims 39-41 have been added which are drawn to subject matter of original claim 8, as it depends on claim 1(a), 1(b), and 1(c) respectively.

Claim 9 has been amended to depend on new claim 38.

Claims 3-6, 8-11, 35 and 36 are pending. The Examiner is requested to also examine new claims 38-41, which is drawn to subject matter originally found in claim 8.

II. The Sequence Listing under 37 C.F.R. §§1.821-1.825

The Examiner fails to comply with the requirements of 37 C.F.R. §§1.821-1.825. Applicants point out that a full response to the sequence listing requirement was filed on April 26, 2002. Submitted herewith is a copy of the stamped USPTO postcard receipt indicating that the statement of equivalence, paper copy of the sequence listing, and diskette, were filed on April 26, 2002. Applicants submit that the application complies with 37 C.F.R. §§1.821-1.825.

The Examiner stated that the sequence shown in Figure 2 must be assigned a SEQ ID NO. The Brief Description of the Drawings at page 10 has been amended to indicate that the sequence shown in Figure 2 is SEQ ID NO:1.

III. Informalities

The Examiner objected to claims 1, 2, 7, 8, and 10-12 as allegedly reciting non-elected inventions and has required "appropriate correction". Applicants respectfully traverse.

In response to the Restriction requirement, claims 1-14, 19, 35, and 36 (Group I) was elected, with Species 1 being provisionally elected. MPEP 806.04(d) states that "once a claim that is determined to be generic is allowed, all of the claims drawn to species in addition to the elected species which include all the limitations of the generic claim will ordinarily be obviously allowable in view of the allowance of the generic claim, since the additional species will depend thereon or otherwise include all of the limitations thereof." MPEP 806.04(f) further states that claims to be restricted to different species must be mutually exclusive, and must recite the mutually exclusive characteristics of such species. Thus, generic claims need not be limited to the elected species, and claims not directed to the elected species need not be cancelled in response to the species election requirement.

IV. Rejection of Claims 1, 2 and 7 Under 35 U.S.C. § 101

The Examiner rejected claims 1, 2, and 7 as being allegedly directed to non-statutory subject matter. Claims 1, 2, and 7 have been cancelled, without prejudice or disclaimer thereof, thus obviating the rejection.

V. Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 1(a), 8, 10, and 11 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not reasonably provide enablement and written description for the use of the nucleic acid as a vaccine or pharmaceutical composition. The Examiner further states that the specification "does not show the nucleic acid to induce a protective immune response that prevents establishment of infection and disease when in any vector or amount of nucleic acid is used to induce an immune response, nor has it been shown to induce a protective immune response to eradicate established pre-existing infection." The Examiner cited a number of

references (Igietseme et al. 2002; Allen et al. 1993; Penttila et al. 2002; Pal et al. 1999; Hechard et al. 2002; Bailey et al. 1993; Stuart et al. 1989; Ellis 1988; Boslego et al. 1991) and concludes that induction of protective immunity is not reasonably predictable. Applicants respectfully traverse.

Contrary to the Examiner's assertion, the specification does show that the described nucleic acid induces a protective immune response that prevents establishment of infection. Example 3, beginning at page 50 of the specification, describes immunization of mice using a DNA construct from which the polypeptide of SEQ ID NO:2 is expressed, *i.e.*, pCAmgp002 (Figure 3). As shown at Table 1 and Figure 4, immunization resulted in immune protection of the mice against an intranasal challenge of *C. pneumoniae*. As evident by the working example, the nucleic acid described in the application is useful for vaccination and the encoded polypeptide does elicit protective immunity in vivo. The fact that protective immunity was obtained is clear evidence that the nucleic acid was targeted to appropriate cell types within the host, became transcriptionally active, and the encoded protein appropriately processed and presented to the host in a manner suitable for recognition by the host's immune system. The specification is therefore fully enabling for the claimed vaccines or compositions, and the inventors have possession of the invention as of the claim date.

In view of the above, Applicants submit that the claims, as amended, comply with 35 U.S.C. § 112, first paragraph, Withdrawal of the rejection is respectfully requested.

VI. Rejection of the Claims Under 35 U.S.C. § 102

The Examiner rejected claims 1, 2, 7, 8, and 10-12 under 35 U.S.C § 102 (a) as being allegedly anticipated by Kalman et al. Applicants traverse this ground for rejection.

Claims 1, 2, 7, and 12 have been cancelled. Claim 8 has been amended to specify that --the nucleic acid molecule is either operatively linked to one or more control sequences for expression of the polypeptide in a mammalian cell, or is

integrated and expressed in a bacterial cell suitable for use as a vaccine vector--. Claim 10 has been amended to specify that --the nucleic acid molecule is operatively linked to one or more control sequences for expression of the polypeptide in a mammalian cell--. Claim 11 depends ultimately on claim 8.

Kalman et al. does not disclose the vaccines and pharmaceutical compositions of the claimed invention. The examiner fails to point where in Kalman it is stated that these proteins were produced recombinantly. Kalman have sequenced the entire genome of two Chlamydia strains by cloning random fragments into a M13 vector for automated sequencing. No expression data is shown. Kalman does not disclose or suggest expressing the sequences. Therefore, Kalman et al.'s sequences lack the structural feature of being operatively linked to one or more control sequences for expression of the polypeptide, as specified Applicants' claims. Since Kalman et al.'s sequences are not in expressible form and are not capable of performing the intended use, Kalman et al. does not anticipate the vaccines and compositions of the claimed invention.

Withdrawal of the rejection under 35 U.S.C. § 102 in view of Kalman et al. is respectfully requested.

VII. Concluding Remarks

In view of the above amendments and remarks, reconsideration and favorable action on all pending claims are respectfully requested. If any questions or issues remain, the Examiner is invited to contact the undersigned at the telephone number set forth below so that a prompt disposition of this application can be achieved.

The Petition for Extension of Time pursuant to 37 CFR 1.136 and the fee are being submitted concurrently with this Response. If a fee is required for an extension of time which is not accounted for above, such an extension is requested and the U.S.P.T.O. is authorized to withdraw from our Deposit Account Number 19-0741 any fee required.

Respectfully submitted,

Date: April 21, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

The paragraph beginning at line 3, page 7, has been amended as follows:

Antigenic variation within the species *C. pneumoniae* is not well documented due to insufficient genetic information, though variation is expected to exist based on *C. trachomatis*. Serovars of *C. trachomatis* are defined on the basis of antigenic variation in the major outer membrane protein (MOMP), but published *C. pneumoniae* MOMP gene sequences show no variation between several diverse isolates of the organism (Campbell *et al.* Infection and Immunity (1990) 58:93; McCafferty *et al* Infection and Immunity (1995) 63:2387-9; Gaydos *et al.* Infection and Immunity.(1992) 60(12):5319-5323). The gene encoding a 76 kDa antigen has been cloned from a single strain of *C. pneumoniae* and the sequence published (Perez Melgosa *et al.* Infection and Immunity.(1994) 62:880). An operon encoding the 9 kDa and 60 kDa ~~cyteine-rich~~ cysteine-rich outer membrane protein genes has been described (Watson *et al.*, Nucleic Acids Res (1990) 18:5299; Watson *et al.*, Microbiology (1995) 141:2489). Many antigens recognized by immune sera to *C. pneumoniae* are conserved across all *chlamydiae*, but 98 kDa, 76 kDa and several other proteins may be *C. pneumoniae*-specific (Knudsen *et al.* Infect. Immun. 1999. 67:375-383; Perez Melgosa *et al.* Infection and Immunity. 1994. 62:880; Melgosa *et al.*, FEMS Microbiol Lett 1993. 112 :199;, Campbell *et al.*, J. Clin. Microbiol. 1990. 28 :1261; Iijima *et al.*, J. Clin. Microbiol. 1994. 32:583). Antisera to 76kDa and 54kDa antigens have been reported to neutralize *C. pneumoniae in vitro* (Perez Melgosa *et al.* 1994. Infect. Immun. 62:880-886 and Wiedman-Al-Ahmad *et al.* 1997. Clin. Diagn. Lab. Immunol. 4:700-704). An assessment of the number and relative frequency of any *C. pneumoniae* serotypes, and the defining antigens, is not yet possible. The entire genome sequence of *C. pneumoniae* strain CWL-029 is now known ~~(http://chlamydia-www.berkeley.edu:4231/)~~ and as further sequences become available a better understanding of antigenic variation may be gained.

The paragraph beginning at line 14, page 10, has been amended as follows:

Figure 2 shows the restriction enzyme analysis of the *C. pneumoniae* OMP (outer membrane protein) gene (SEQ ID NO:1).

The paragraph beginning at line 1, page 22, has been amended as follows:

A recombinant expression system is selected from procaryotic and eucaryotic hosts. Eucaryotic hosts include yeast cells (*e.g.*, *Saccharomyces cerevisiae* or *Pichia pastoris*), mammalian cells (*e.g.*, COS1, NIH3T3, or JEG3 cells), arthropods cells (*e.g.*, *Spodoptera frugiperda* (SF9) cells), and plant cells. A preferred expression system is a procaryotic host such as *E. coli*. Bacterial and eucaryotic cells are available from a number of different sources including commercial sources to those skilled in the art, *e.g.*, the American Type Culture Collection (ATCC; ~~Rockville, Maryland~~ 10801 University Boulevard, Manassas, VA 20110-2209). Commercial sources of cells used for recombinant protein expression also provide instructions for usage of the cells.

The paragraph beginning at line 26, page 48 has been amended as follows:

The OMP (outer membrane protein) gene (SEQ ID NO:1) was amplified from *Chlamydia pneumoniae* genomic DNA by polymerase chain reaction (PCR) using a 5' primer
(5' ATAAGAATGCGGCCGCCACC**ATGGGACTATTCCATCTAACTCTC** 3'; SEQ ID No:3) and a 3' primer
(5' GCGCCGGATCCC**CTCCACAATTTTTATGAGTAAGCC** 3'; SEQ ID No:4). The 5' primer contains a Not I restriction site, a ribosome binding site, an initiation codon and a sequence at the 5' end of the OMP (outer membrane protein) coding sequence. The 3' primer includes the sequence encoding the C-terminal sequence of the OMP (outer membrane protein) and a Bam HI restriction site. The stop codon was excluded and an additional nucleotide was inserted to obtain an in-frame fusion with the Histidine tag.

The paragraph beginning at line 14, page 49 has been amended as follows:

Plasmid pcDNA3.1(-)Myc-His C (Invitrogen) was restricted with Spe I and Bam HI to remove the CMV promoter and the remaining vector fragment was isolated. The CMV promoter and intron A from plasmid VR-1012 (Vical) was isolated on a Spe I / Bam HI fragment. The fragments were ligated together to

produce plasmid pCA/Myc-His. The Not I/Bam HI restricted PCR fragment containing the OMP (outer membrane protein) gene (SEQ ID NO:1) was ligated into the Not I and Bam HI restricted plasmid pCA/Myc-His to produce plasmid pCAmgp002 (Figure 3).

IN THE CLAIMS:

The first line in the claims page has been amended as follows:

~~Claims~~ What is claimed is:

IN THE CLAIMS:

Claims 8-11 have been amended as follows:

8. (Amended) A vaccine comprising ~~at least one first nucleic acid according to claim 1, and a vaccine vector wherein each first nucleic acid is expressed as a polypeptide, the vaccine optionally comprising a second nucleic acid encoding an additional polypeptide which enhances the immune response to the polypeptide expressed by said first nucleic acid~~ a vaccine vector wherein the vaccine vector comprises a nucleic acid molecule which encodes a polypeptide selected from any one of:

(a) SEQ ID No: 2;

(b) an immunogenic fragment comprising at least 12 consecutive amino acids from SEQ ID No: 2; and

(c) the polypeptide of (a) or (b) which has been modified by conservative amino acid substitution without loss of immunogenicity, wherein said modified polypeptide is at least 75% identical in amino acid sequence to the corresponding polypeptide of (a) or (b);

wherein the nucleic acid molecule is either operatively linked to one or more control sequences for expression of the polypeptide in a mammalian cell, or is integrated and expressed in a bacterial cell suitable for use as a vaccine vector.

9. The vaccine of claim ~~8~~ 38 wherein the second nucleic acid encodes an additional *Chlamydia* polypeptide.

10. (Amended) A pharmaceutical composition comprising ~~a nucleic acid according to claim 1 and~~ a pharmaceutically acceptable carrier or diluent suitable for use in a vaccine and a nucleic acid molecule comprising a nucleic acid sequence which encodes a polypeptide selected from any one of:

(a) SEQ ID No: 2;

(b) an immunogenic fragment comprising at least 12 consecutive amino acids from SEQ ID No: 2; and

(c) the polypeptide of (a) or (b) which has been modified by conservative amino acid substitution without loss of immunogenicity, wherein said modified polypeptide is at least 75% identical in amino acid sequence to the polypeptide of (a) or (b);

wherein the nucleic acid molecule is operatively linked to one or more control sequences for expression of the polypeptide in a mammalian cell.

11. (Amended) ~~A pharmaceutical composition comprising a~~ The vaccine according to claim 8 ~~and~~ further comprising a pharmaceutically acceptable carrier.